

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIPHENYLAMINE

Chemical Code # 000228, Tolerance # 00190
SB 950 # 308

September 1, 1987

Revised 9/6/88; 7/26/89; 10/01/93; 7/24/95; 8/08/96

I. DATA GAP STATUS

Combined rat (chronic + oncogenicity):	No data gap, possible adverse effect
Chronic dog:	No data gap, possible adverse effect
Oncogenicity mouse:	No data gap, no adverse oncogenic effect
Reproduction rat:	No Data gap, no adverse effect
Teratology rat:	No Data gap, no adverse effect
Teratology rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect

Chromosome: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotox: Not required at this time

-----**Note, Toxicology**
one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect

File name = T960808
Revised by M. Silva, 9/88; J. Gee, 7/26/89; P. Iyer, 10/01/93; 7/24/95; 8/8/96
All record numbers through 143874 were examined.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

PLEASE NOTE: It is imperative that the test article(s) employed in any toxicity studies be the technical material(s) of commerce for which registration(s) is/are sought. Investigators in several studies have noted that impurities, including aniline and/or analogs, may be responsible for some of the effects observed in some of the older studies. It is also necessary to establish whether technical materials decompose during storage to form significant amounts of toxic products. Aldous, 9/1/87.

COMBINED, RAT

****015** 017 018 021 **132532** 143867 143868 and 143872, "24 Month Combined Oncogenicity/Toxicity Evaluation of Diphenylamine in Rats", (J.A. Botta, Jr., T.P.S., Inc., 426D-102-048-91, 9/27/94). Diphenylamine technical, purity >97%, administered orally in feed to Sprague-Dawley rats (60/sex/group), at concentrations of 0, 200, 750, 3750 and 7500 ppm (males), and 0, 150, 500, 2500 and 5000 ppm (females) for 24 months. Reduced body weight and increased spleen weight were noted at the two high dose groups. At week 102: **reduction in red blood cells** (males 750 ppm and above, females 2500 ppm and above) was observed; globulin levels were decreased (males - 3750 and 7500 ppm, female - 5000 ppm). Non-neoplastic findings (considered compensatory changes of RBC reduction) noted for the **three high dose groups** of both sexes were **congestion, hemosiderosis, hematopoiesis of the spleen, erythroid hyperplasia of bone marrow, hematopoiesis in liver and presence of pigment in liver and kidney**. CHRONIC NOEL = 150-200 ppm/day (reduction in RBC count and presence of brown pigment in kidney and liver). No treatment-related neoplastic lesions. Previously reviewed to be unacceptable, (Kishiyama, J. and Iyer, P. 7/23/95) upgradeable upon submission of data on stability of test article in the diet and dose-level justification. Data from subchronic study (018 143868) and supplementary studies 017 143867, 021 143872 upgrade the study to ACCEPTABLE. (Iyer, P. 5/3/96).

190-017 143867, "Evaluation of Homogeneity and Stability of Diphenylamine in Prepared rodent Diets" (R.C. Hatch., T.P.S., Inc., 426F-999-999-91, 8/14/91). Diphenylamine (99.6%), dissolved in warmed corn oil and mixed at concentration of 0, 10, 500, 3000 and 15000 ppm in certified rodent meal, was analysed in duplicate for diphenylamine homogeneity and stability by an HPLC method. Samples of each stored diet were taken at 8, 15, 22, 29 and 36 days after mixing. Mean concentrations of diphenylamine were within 10% of theoretical in the 8 day samples when stored in sealed containers (Table 2 page 17). Variations in concentrations were noted after the 8 day period which have been attributed to chance sampling error resulting in concentrations less than 10% of the theoretical. Overall findings indicate that diphenylamine in concentrations up to 15000 ppm was stable for 8 days in certified rodent meal stored in sealed containers or exposed to the animal room environment (Table 3, page 18). Supplemental information, useful in upgrading the combined (chronic & Oncogenicity) rat study (015 132532) to acceptable status (P. Iyer, 5/3/96).

190-018 143868, "90 Day Subchronic Toxicity Evaluation of Diphenylamine in Rats" (R.W. Krohmer., T.P.S., Inc., 426C-101-034-91, 5/20/92). Diphenylamine technical, purity >99%, administered orally in feed to Sprague-Dawley rats (10/sex/group), at concentrations of 0, 150, 1500, 7500 and 15000 ppm for 90 days. No treatment-related effect on ophthalmology or food consumption. A dose-dependent, treatment-related effect was seen with a significantly reduced erythrocyte count and hemoglobin concentration at the 1500 (females), 7500 and 15000 ppm group. Similarly, a greenish tint to the hair was noted in the mid-to-high dose groups, also suggestive of a dose-dependent pattern beginning week 11. Reduction in body weight without a significant reduction in food consumption was noted at the 7500 ppm group and higher all through the study beginning in Week 1. Also animals in these two groups (7500 and 15000 ppm) had an increased incidence of hematopoiesis in the liver, spleen and bone marrow. Congestion and hemosiderosis in the spleen as well as pigment in the reticuloendothelial cells in the liver and in the convoluted tubular epithelial cells in the kidneys were also noted in animals at 7500 and 15000 ppm. Increases in liver and spleen weights (absolute and relative) were noted in both sexes of the two high dose groups and an increase in spleen weights was noted in females of the 1500 ppm group. The findings support a NOEL = 150 ppm (males: 9.6 mg/kg/day; females: 11.5 mg/kg/day) and suggest that the females are more sensitive to

diphenylamine than the males, probably due to a higher food consumption which in turn would result in a higher available dosage to females. Data from this study provides dose-level justification required to upgrade the combined (chronic & Oncogenicity) rat study (015 132532) to acceptable status (P. Iyer, 5/3/96).

021-143872 "Diphenylamine: Rat Metabolism Study" Diana Wu, XenoBiotic Laboratories Inc. Plainsboro, NJ., XBL Report No. RPT00131. 10/27/93. A rat metabolism study according to FIFRA guidelines was conducted by administering male and female Sprague-Dawley rats a single oral low dose (SOLD) and a single oral high dose (SOHD) of ¹⁴C-diphenylamine at 5 and 750 mg/kg respectively. Also 10 animals were dosed once daily for 14 days with 5 mg/kg (MOLD) of unlabeled diphenylamine following a single dose of the radiolabeled chemical on day 15. Urine and feces were collected over 7-day intervals and excreta and tissues from sacrificed animals were analyzed for radioactivity content. Diphenylamine is rapidly absorbed orally and excreted within the first 24-48 hours after dosing. Diphenylamine appears to undergo extensive biotransformation (only a small amount of parent compound is found in feces) mainly consisting of oxidation/hydroxylation, primarily on the para-position of the phenyl moiety, followed by conjugation with sulfonic acid and glucuronic acid. Further hydroxylation to form dihydroxylated metabolites was also observed. The majority of the metabolites were found in the urine (as sulfate and glucuronide conjugates), which was the major route of excretion. 4-OH-DPA-O-sulfonic acid and 4-OH-DPA-O-glucuronic acid were the major metabolites ranging from 2.06% to 43.91% of the administered dose (page 16). At the high dose male rats excreted more of the administered dose in feces than females, while at the low dose (SOLD & MOLD) female rats excreted more of the administered dose in the feces. Indophenol the metabolite supposedly responsible for staining the fur green was not a major metabolite and was found to be in the range of 0.18 - 0.59% of the administered dose. No worksheet. Supplemental study (Iyer, 5/30/96).

CHRONIC, RAT

003 035397 "Chronic Toxicity of Diphenylamine to Albino Rats" (Toxicology and Applied Pharmacology 10 1967: 362-374), Western Regional Research Lab., Albany, CA; Diphenylamine (DPA--99.9% purity, grade unknown) in the diet of Slonacker-Addis albino rats (0, 10, 100, 1000, 5000 & 10000 ppm) to 20 rats/sex/group; Apparent NOEL = 1000 ppm (reduced weight gain, kidney "chronic nephritis" and cystic dilatation of renal tubules) but insufficient information for independent review; Incomplete (journal article); UNACCEPTABLE (insufficient number of animals, too few parameters studied). CDFA review by C. Aldous 10/30/85.

001 022064 Exact duplicate of record #035397 in volume 190-003.

001 034853 "Perinatal Nephropathies" (Environmental Health Perspectives 15 1976: 121-130); Literature review of chemically induced renal anomaly data; Long-term feeding of Diphenylamine to the adult rat was noted to cause cystic kidney disease, loss of concentrating ability in the kidney, dilatations in collecting ducts of the kidneys [Safouh et. al., Lab. Invest. 23:392 (1970)]; Insufficient information for independent review of adverse effects; UNACCEPTABLE--Very Brief Summary (10 page journal article, only limited discussion of diphenylamine). CDFA review by J. Remsen 8/21/85.

A statement in 008, dated April 12, 1989, indicates NTP will be conducting a rat study. Gee, 7/25/89.

CHRONIC, DOG

****012, 019, 020 127226, 143869, 143871**, "One Year Chronic Study of Diphenylamine in Dogs", (J.A. Botta Jr., T.P.S. Inc., IN. Laboratory Project I.D. 426B-502-044-91, 10/28/93). Diphenylamine (purity 99%), was administered by gelatin capsules at concentrations of 0, 10, 50 or 100 mg/kg/day to 4 Beagle dogs/sex/group for 52 weeks. NOAEL <10 mg/kg (**elevated bilirubin** with statistical significance, at 26 weeks in the male, and both 26 weeks and 39 weeks in the female for the 10 mg/kg/day group). Previously reviewed as unacceptable (Kishiyama, J., and Iyer, P., 7/23/95). Submission of range-finding studies (019, 020 143869,

143871) provide the rationale for dose selection, changing status to ACCEPTABLE. (P. Iyer, 6/5/96).

Note: Bilirubin was not elevated at 90 days in the subchronic study, #143871, at doses up to 50 mg/kg/day.

** 020 143871, "90 Day Subchronic Toxicity Evaluation of Diphenylamine in Dogs" (R.W. Krohmer, T.P.S. Inc., IN. Laboratory Project I.D. 426A-501-034-91, 12/6/91). Diphenylamine (purity 99%), was administered by gelatin capsules at concentrations of 0, 5, 25, or 50 mg/kg/day to 4 Beagle dogs/sex/group for 90 days. No treatment-related changes in body weight, body weight change, food consumption, urine analysis, hematology, clinical chemistry, organ weights or ophthalmological exam were noted. No mortality was noted and necropsy findings revealed no treatment-related gross or histopathological changes. Since no changes in clinical or anatomical pathology were noted, the highest dose level of 50 mg/kg/day would qualify as the NOEL. Acceptable. No worksheet (P. Iyer, 6/5/96).

019 143869, "28 Day Range-finding Evaluation of Diphenylamine in the Dog", (R.W. Krohmer, T.P.S. Inc., IN. Laboratory Project I.D. 426G-503-020-91, 5/20/92). Diphenylamine (purity 99%), was administered by gelatin capsules at concentrations of 125, 250 or 500 mg/kg/day to 2 Beagle dogs/sex/group for 28 days (no control group). Consistent changes between pretest and termination values were noted for all groups for numerous hematology and clinical chemistry parameters and organ weights for spleen and liver. All groups were affected to some degree and in some instances a direct correlation of severity to the dose level was observed. At necropsy, all dogs demonstrated a thickening of the lower intestinal wall and at least one animal/group had red mucoid material in some portion of the gastrointestinal tract. Histological evaluation of a limited list of tissues found all animals exhibiting minimal to slight inflammation of some parts of the G.I. tract (enteritis in duodenum, jejunum, ileum; cecitis, colitis in colon and rectum). The study suggests that the NOEL for diphenylamine is less than the lowest dose (125 mg/kg/day) tested. No worksheet. Supplemental (P. Iyer, 6/5/96).

003 035398 "The Chronic Toxicity of Diphenylamine for Dogs," (Toxicology and Applied Pharmacology 11 1967: 184-194), Western Regional Research Lab., ARS-USDA, Albany, CA; Diphenylamine (99.9% purity, grade unknown in the diet at 0, 0.01, 0.1 or 1.0 percent (100, 1000 or 10000 ppm) for 2 years to 2 dogs/sex/group; NOEL apparently 1000 ppm (fatty liver, signs of liver damage, anemia (reduced hemoglobin, reduced erythrocyte count) all at 10,000 ppm, however, insufficient information for independent review; Incomplete (journal article); UNACCEPTABLE (insufficient number of animals, too few parameters studied). CDFA review by C. Aldous 10/31/85.

001 022065 Exact duplicate of record #35398 in volume 190-003.

CHRONIC, MOUSE

****014 022 023, 131986 143873 143874**, "18 Month Oncogenicity Evaluation of Diphenylamine in the Mouse", (J. A. Botta, Jr., T.P.S., Inc., IN., Report # 426H-002-646-91, 8/24/94). Swiss derived CD-1 mice 60/sex/group received 0, 525, 2625, or 5250 ppm of test article identified as diphenylamine (> 99% purity) in the diet for 18 months. 10/sex/group were necropsied at 12 months. Red blood cell (RBC) and hematocrit values were reduced while mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were increased for mid and high dose males and females after 52 and 78 weeks. Spleen weights relative to bodyweight were increased (50% to 550%) compared to controls at the interim and terminal necropsies for both sexes at mid and high dose levels and for low dose females (87%) at the interim sacrifice. **Possible adverse effects (non-oncogenic) were noted: congestion and hemosiderosis of spleen at all treatment levels.** Chronic NOEL < 525 ppm (splenic changes of congestion and hemosiderosis for all treatment groups considered physiological compensation by author). Green tinted hair and urogenital staining were noted at 525 ppm and higher levels. Chronic NOAEL = 525 ppm (increased mortality, **amyloidosis in females and cystitis in males**). Oncogenicity NOEL > 5250 ppm. Previously reviewed as unacceptable (H. Green, and P. Iyer, 7/24/95). Upgradeable upon submission of data on the analysis of the test material and the 90 day subchronic study provides information for the

dosing rationale and test article characteristics. These data (022 023 143873 143874) upgrade the study to acceptable (P. Iyer, 6/7/96).

023 143874, 90 Day Subchronic Toxicity Evaluation of Diphenylamine in Mice

(J. A. Botta, Jr., T.P.S., Inc., IN., Report # 426E-001-034-91, 10/19/92). Swiss derived CD-1 mice 15/sex/group received 0, 10, 525, 2625, or 5250 ppm of test article identified as diphenylamine (> 99% purity) in the diet for 90 days. No effect on animal survival, mean body weight, mean body weight change or ophthalmology was noted. Red blood cell (RBC) and packed cell volumes were reduced while mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were increased for 2625 and 5250 ppm levels. Greenish tint of hair at 2625 and 525 ppm was considered by author to be due to external contact with a metabolite of diphenylamine rather than a systemic effect. Necropsy revealed **enlarged darkened spleens and/or livers in the three high dose groups**, increased heart and kidney weights (absolute and relative) at the highest dose and decreased ovarian weights in females at all 4 treated groups. Histopathology revealed **increased splenic hematopoiesis at the two high dose groups and urocystitis at the highest dose**. NOEL = 10 ppm. No worksheet (P. Iyer, 6/7/96).

002 035393 "Heinz Body Formation--Long-Term Study of DPA in Mice," Literature review, Pennwalt Corp. describes several feeding studies in which mice or rats were administered various levels of technical diphenylamine (of various sources) in their diets; Heinz bodies (thought to be aggregates of precipitated, denatured hemoglobin) were observed in blood of mice fed 50 ppm and greater levels of diphenylamine. There was no NOEL for mice, due to these blood effects, however the degree of effect at 50 ppm was probably not functionally important. Rats were apparently less affected than mice. Insufficient information for independent review. Pennwalt Corp. maintains that removal of aniline and other related primary amines as contaminants from commercial diphenylamine would minimize this adverse effect; Very Brief Summaries; **Not a Required Study**. CDFA review by C. Aldous, 11/1/85.

ONCOGENICITY--RAT

001 022063 "On the Carcinogenicity of a Single Intragastric Dose of Hydrocarbons, Nitrosamines, Aromatic Amines, Dyes, Coumarins, and Miscellaneous Chemicals in Female Sprague-Dawley Rats" (Cancer Research 25 April, 1966: 619-625) Southern Research Institute & Birmingham Baptist Hospital, Birmingham, Alabama/NCI; Carcinogenicity of diphenylamine (300 mg/kg) determined 6 months following a single oral administration of 300 mg/kg to 20 female Sprague-Dawley rats. No adverse effects observed in this study. **Not a Required Study, not acceptable by chronic/oncogenicity study guidelines, no further information required of this study.** C. Aldous, 8/28/87.

ONCOGENICITY, MISCELLANEOUS

002 035392 Mutagenicity--Carcinogenicity Brief literature review by Pennwalt Corp. of carcinogenicity tests of diphenylamine (DPA) impurities 2-aminobiphenyl, 4-aminobiphenyl and aniline; Oncogenic effect noted in 4-aminobiphenyl study; 2-aminobiphenyl and aniline studies noted as containing inadequate data; Literature references not clearly given; UNACCEPTABLE--Insufficient information to review, Very Brief Summaries. CDFA review by C. Aldous 11/1/85.

REPRODUCTION, RAT

** 011 121052, "Two Generation Reproduction Study in Rats with Diphenylamine (DPA)", (D.E. Rodwell, Springborn Laboratories Inc., SLS Study No. 3255.4, 1/14/93). Diphenylamine, purity 99.9%, admixed with rodent meal at concentrations of 0, 0.05, 0.15 and 0.50%, was fed to two generations of 28 Sprague-Dawley rats/sex/group. Reproductive NOEL = 0.15% DPA/day based on reduced (21%) F2 litter size. Systemic NOEL = 0.05 % based on clinical observations. Pup body weight was lower for the F1 group, near birth (11% lower on day 1) and during lactation at the high dose level, and also for the F2 group during lactation at the mid and high dose levels. Parental F0 and F1 groups had lower body weight, body weight gains and food consumption were lower at the mid and high dose levels. Spleens turned blackish-purple and were heavier at mid and high dose levels, in addition to splenic congestion and hemosiderosis at all doses.

Relative weights of liver and kidneys was increased at mid (female) and high dose levels (male and female). Hepatocyte hypertrophy, brown pigment in Kupffer cells and hemosiderosis in the proximal renal tubular epithelium were observed at 0.15 and 0.50 % levels. The incidence of bluish stained fur was increased at the high dose levels. ACCEPTABLE. (Kishiyama, J. and Iyer, P., 9/21/93).

003 055540 "Chronic Toxicity of Diphenylamine to Albino Rats" [Ancillary Reproduction Study] (Toxicology and Applied Pharmacology 10 1967: 362-374), Western Regional Research Lab., Albany, CA; Diphenylamine (DPA--99.9% purity, grade unknown), 0, 1000, 2500 and 5000 ppm in the diet; 12 females and 3 males per dose group, First generation--2 litters, Second generation--one litter; Possible reduction in litter size at 5000 ppm, but findings are neither consistent nor dose-related; Incomplete (journal article); UNACCEPTABLE (insufficient numbers of animals, other deficiencies: upgrade not possible). CDFA reviews by C. Aldous 10/30/85 and 8/31/87.

Note: this reproduction "study" is a minor segment of the report, which is almost entirely devoted to the chronic effects study. Previous review of 003:035397 noted "smaller litter size at 5000 ppm" in the ancillary reproduction study. On re-review, this does not merit flagging a "possible adverse health effect" because (a) there is no consistent, dose-related effect, and (b) the dose level at which this questionable observation was made is demonstrably maternally toxic in the chronic portion of the study. Aldous, 9/87.

TERATOGENICITY, RAT

** 010 114219, "Teratology Study in Rats with Diphenylamine (DPA)", (D.E. Rodwell, Springborn Laboratories, Inc., SLS Study No. 3255.3, 4/13/92). DPA, purity 99.9%, administered by gavage at concentrations of 0 (Mazola* oil), 10, 50, 100 mg/kg to 25 Sprague-Dawley mated female rats/group on days 6 through 15 of gestation. During the initial 3 days of treatment, food consumption and body weight gain were lower for the high dose group. The 100 mg/kg exposure group demonstrated a highly significant decrease ($P < 0.01$) in food consumption and body weight gain during the entire period of exposure. A similar decrease in body weight gain was observed

at the 10 mg/kg and 50 mg/kg ($P < 0.05$) but not to the same extent. In the high dose group, maternal spleen weight was increased (135%) and the spleens of some of the high dose animals (5/25 i.e. 20 %) were enlarged and blackish-purple. No significant increase or treatment induced malformations or developmental variations were reported for this study. Maternal NOEL = 50 mg/kg; Nominal Developmental NOEL \geq 100 mg/kg/day. The splenomegaly and possible hemosiderosis (lack of confirmatory histopathology) along with the history of Heinz bodies observed in the chronic study could be indicative of some level of hemolytic disease and maternal toxicity. ACCEPTABLE. (Kishiyama, J., and Iyer, P., 9/10/93).

009 114218, "Range-Finding Teratology Study in Rats with Diphenylamine (DPA)", (D.E. Rodwell, Springborn Laboratories, Inc., SLS Study No. 3255.2, 4/13/92). DPA, purity 99.9%, administered by gavage at concentrations of 0 (Mazola* oil), 50, 100, 200, 300 or 400 mg/kg to 6 Sprague-Dawley mated rats/group on days 6 through 15 of gestation. Body weight gain and food consumption were reduced at 100 mg/kg and higher levels during the first 3 days of treatment and throughout the treatment period for the two highest dose levels. Spleens became enlarged and blackish-purple at the 3 highest dose levels. **Possible adverse effect: maternal mortality and total litter resorptions increased at 400 and 300/400 mg/kg dose levels, respectively.**

Based on these results, dose levels of 10, 50 and 100 mg/kg were selected for the main teratology study. (Kishiyama, J. and Iyer P., 9/10/93).

DPA when fed to pregnant rats, has been reported to produce polycystic kidneys. However, McCormack et al., (Toxicology of the Kidney. Raven Press, NY, 1981, pp227-50) suggest that this might not constitute permanent structural damage and only reflect delayed maturation. In the current study since there was no evidence of kidney lesions at any of the exposure levels, and a maternally toxic level was documented, this finding is perhaps not relevant.

001 034853 "Perinatal Nephropathies" (Environmental Health Perspectives 15 1976: 121-130); [Classified as a rat teratogenicity report] Literature review of chemically-induced renal anomaly data; Diphenylamine fed to pregnant rats during the last week of gestation at 2.5% in the diet resulted in dilatation of the renal tubules with cystic lesions in proximal portion of nephron (Crocker et. al. Ped. Clin. N. Amer. 18:355, 1971). The dose level was well into the range of adult toxicity, hence study **did not** indicate a significant adverse

developmental toxicity effect. CDFA review by J. Remsen 8/21/85 indicated possible developmental toxicity effect. Re-examination of publication by C. Aldous on 9/1/87 removed "possible adverse health effects" flag, as indicated above.

The NTP has decided not to undertake the study it had previously proposed (Tox Summary, 1989) and has deferred it to be conducted by industry instead (Iyer, P., 9/13/93 - telephone communication).

TERATOGENICITY, RABBIT

** 002, 008 035374, 073917 "Effect of Diphenylamine on Pregnancy of the New Zealand White Rabbit," Huntingdon Research Centre, Huntingdon, England, 6/17/83. Diphenylamine (99.9%, Pennwalt commercial grade) at 0, 33, 100 or 300 mg/kg by oral gavage days 7-19 of gestation to 16-18 New Zealand White rabbits/group. Maternal NOEL = 300 mg/kg/day, (decreased food consumption and related slight decrease in body weight gain in early part of pregnancy). Developmental toxicity NOEL = 300 mg/kg/day (HDT). Not acceptable, but upgradeable (dosing solution analysis needed: see 9/1/87 review). Earlier review (11/1/85) rejected the study primarily for insufficient dosage. Re-reading of report found the high dose adequate because modest decrease in food consumption and decreased body weight gains appear to have been true treatment effects, although not necessarily toxicity-related. CDFA reviews by C. Aldous, 11/1/85 and 9/1/87. Record # 073917 contains retrospective analyses of dosing solutions prepared from the same batch of diphenylamine. Study is upgraded at this time to ACCEPTABLE status. Gee, 7/25/89.

MUTAGENICITY, MISCELLANEOUS

002 035388-035391 "Mutagenicity"--Various, Brief literature review by Pennwalt Corp. of 5 mutagenicity tests of Diphenylamine (DPA), and a mutagenicity test each on DPA impurities 2-aminobiphenyl, 4-aminobiphenyl and aniline; Literature references not clearly given; No

adverse effects noted in cited DPA summaries, Mutagenicity noted in DPA impurity studies;
UNACCEPTABLE--Insufficient information to review, Very Brief Summaries. CDFA review by C.
Aldous 11/1/85.

GENE MUTATION

** 005 067477 "Ames Salmonella/Microsome Plate Test (EPA/OECD)," (Pharmakon Research International, Inc., 3/15/85). Diphenylamine (purity not stated), was tested in a mutagenicity assay with and without activation on TA1535, TA1537, TA1538, TA98 and TA100 at 0 (vehicle = acetone), 1.0, 3.3, 10, 33, and 100 ug/plate (triplicate plates). No adverse effect. No mutagenesis was observed at any dose with any of the tester strains. The positive controls functioned as expected. ACCEPTABLE. M. Silva, 9/1/88.

STRUCTURAL CHROMOSOME ABERRATION

** 005 067478 "Micronucleus Test (MNT) OECD," (Pharmakon Research International, Inc., 1985). Diphenylamine technical (purity not stated) was administered i.p. to Cd-1 mice at 0 (vehicle = corn oil) and 750 mg/kg. Mice (5/sex/time point) were sacrificed and cells were harvested at 30, 48 and 72 hours (treatment groups) or 48 hours (negative control). No adverse effect. No increase in micronuclei was observed in the treated animals at any time point. The positive control functioned as expected. ACCEPTABLE, M. Silva, 9/1/88.

OTHER GENOTOXIC EFFECTS/DNA DAMAGE

** 005 067479 "Rat Hepatocyte Primary Culture/DNA Repair Test," (Pharmakon Research International, Inc., 6/21/85). Diphenylamine technical (purity unknown) was used on primary hepatocyte cultures from male Fischer 344 rats at 0, 0.33, 1.0, 3.3, 10, 33, 100, 333, 1000, 3333 and 10,000 ug/dish for 18-20 hours. 60 cells/culture dish were counted for unscheduled DNA synthesis. No adverse effect. No unscheduled DNA synthesis was observed at any dose level. Toxicity was observed at levels \geq 333 ug/well. The positive control functioned as expected. ACCEPTABLE. M. Silva, 9/2/88.

NEUROTOXICITY

Not required at this time.

MISC. GENERAL REPORTS: ALL CATEGORIES

("For Your Information" submissions: not data requiring formal CDFA review)

003 035401-035404 Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues, Rome (excerpts from various reports, 1969-1984); Literature review of short-term, long-term and special studies of diphenylamine; Adverse effects identified in the areas of chronic toxicity (anemia; liver, kidney and spleen effects) and reproductive toxicity (kidney effect, unknown impurity implicated) but insufficient information for independent review. CDFA "review" by C. Aldous, 10/30/85.

001 055449 "Diphenylamine, Fragrance Raw Materials Monographs, 1978", (Opdyke, et. al., Food Cosmet. Toxicology 16 1978: 723-727) Literature review, Possible adverse effects identified in the areas of chronic toxicity (kidney) and teratogenicity (effects of aged diphenylamine studied; kidney abnormalities) but insufficient information for independent review (no CDFA review).

SUPPLEMENTAL

022 143873, "Analysis of Diphenylamine: Interim Report" MRI Project No: 9919-F, (A. Clark 6/8/92). Submitted by J. Wise and Associates, MO. A report on the analyses performed by Midwest Research Institute (MRI) for diphenylamine (DPA), to provide analytical chemistry support for toxicology studies and consisted of identification and purity analyses for three batches of diphenylamine. Each batch of material was identified as diphenylamine by nuclear magnetic resonance (NMR) spectroscopy. Additionally, high-performance liquid chromatographic (HPLC)

impurity profiling of each batch revealed a major peak ($101.5\% \pm 0.3$, $100.8\% \pm 0.3$ and $102.0\% \pm 0.3$ relative to a DPA standard) and one small impurity, less than 0.1% relative to major peak (pp 27-29). No worksheet. Supplemental. No worksheet (P. Iyer, 6/10/96).